REMARKS

I. Claim amendments

Claims 1, 18, 26 and 27 have been amended to clarify that the recited formulation is administered at least twice with a 0.5-4 hour interval between at least two consecutive administrations in accordance with the claimed method.

In the Office Action at page 2, the Examiner states that the claims still contain the term comprising which was agreed, as stated in the Interview Summary, to be changed to consisting. Applicants respectfully submit that the claims were previously amended in the manner as agreed upon during the Examiner Interview of 12 February 2003 and as summarized in the Interview Summary. Specifically, it was agreed that the method claim would be re-written in Jepsom form to define the invention in terms of the improvement of which the claimed method "consisted". Thus, for the record, the claims were amended by the Amendment, filed 8 April 2003, in the manner which Applicants understood to have been agreed upon during the Examiner Interview.

Nevertheless, in the spirit of cooperation, claims 1, 18, 26 and 27 have been amended to recite that the recited the H^+, K^+-ATPase inhibitor is the ***only*** active ingredient of the formulation to be administered in accordance with the claimed invention. "Comprising" language is required to properly define the recited formulation which must include pharmaceutically acceptable excipients as well as the ***sole*** active ingredient.

Applicants submit that the amended claims are fully supported by the original disclosure and that no new matter has been introduced.

II. Claim Rejection – 35 U.S.C. §112

Claims 1, 18, 26 and 27 are rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

On page 4 of the final Office Action, the Examiner states that the previously amended claims "do not clearly indicate the 0.5-4 hour interval". Applicants submit that the claims as amended by this Amendment clearly provide that the recited formulation is administered at least twice with a 0.5-4 hour interval between consecutive administrations in accordance with the claimed method. Withdrawal of the §112 rejection is requested.

III. Claim Rejection – 35 U.S.C. §102

Claims 1, 2, 18, 26 and 27 remain rejected under 35 U.S.C. §102(b) in view of Martindale: The Extra Pharmacopoeia 13th Ed. (1993) ("Martindale") for the reasons of record..

A. Martindale discloses "daily" or "twice daily" doses of omeprazole.

Under the heading "Uses and Administrations", Martindale discloses the following administration regimens:

- the usual dose for healing of reflux oesophagitis is 20 to 40 mg ***once daily*** for 4 to 8 weeks; thereafter maintenance therapy can be continued with 20 mg ***daily***;
- in the management of peptic ulcer a ***single daily dose*** of 20 to 40 mg is recommended; and
- the initial recommendation dosage for patients with the Zollinger-Ellison syndrome is 60 mg ***once daily***, but doses in the range 20 to 120 mg ***daily*** may be used; doses above 80 mg should be divided and given ***twice daily***.

B. Martindale does not disclose an administration regimen with 0.5-4 hour intervals.

The claimed invention is defined by at least two consecutive administrations of the recited formulation with 0.5- 4 hour intervals between consecutive administrations. In the absence of impermissible hindsight, the disclosure by Martindale of "daily" or "twice daily" administrations does not disclose or suggest the interval of 0.5-4 hours as recited by the claimed method.

As shown above in Section III(A), above, the weight of the teaching by Martindale is a single daily dose of omeprazole. Martindale expressly states that the treatment of Zollinger-Ellison syndrome may present an ***exception*** to the standard administration regimen of a single daily dose. Specifically, the initial recommended dosage for patients with the Zollinger-Ellison syndrome is 60 mg once daily. The exception is the dividing of larger doses, e.g., above 80 mg, which may be administered twice daily.

Furthermore, the Examiner's attention is directed to the discussion appearing in Chisum on Patents, Chapter 3, Novelty, §3.02[2] - Genus and Species - Combination ("Chisum"), and the cited cases which support the novelty of the claimed invention in view of Martindale. Specifically, the relevant law is summarized by Chisum as follows:

> It is well settled that a valid patent may issue for a nonobvious improvement on a prior patented invention, even though the improvement falls within the claims of that prior patent. This suggests that ***a prior genus which does not explicitly disclose a species does not anticipate a later claim to that species***. The genus, if later, would not infringe the species claim, at least not in all cases. Hence, it does not anticipate. (Citations omitted).

It is readily evident that Martindale does not explicitly disclose the administration interval of 0.5-4 hours as claimed. Therefore, Applicants rely on Chisum, and the case law cited

therein, and submit that Martindale does not anticipate the claimed invention.

For all of the foregoing reasons, withdrawal of the §102 rejection.

IV. Claim Rejection – 35 U.S.C. §103

Claims 1, 2, 18, 26 and 27 remain rejected under 35 U.S.C. §103 in view of US 5,330,982 to Tyers ("Tyers") for the reasons of record. The Examiner alleges that Tyers teaches an administration regimen of 1 to 4 times a day of an H^+, K^+-ATPase inhibitor.

A. An administration regimen of 1 to 4 times per day is different from and does not suggest an administration regimen having 0.5-4 hour intervals.

Applicants respectfully submit the following:

- an administration regimen of 1 to 4 times per day is different from an administrative regimen having 0.5-4 hour intervals between at least two consecutive administrations; and
- in the absence of impermissible hindsight, an administration regimen of 1 to 4 times per day does not suggest an administrative regimen with 0.5-4 hour intervals between at least two consecutive administration.

In general, the prior art regimen of 1 to 4 times a day is typical for many prescribed drugs. It is an administration regimen that is very different from a regimen, as recited by the claimed invention, having 0.5-4 hour intervals between at least two consecutive administrations. Moreover, in the absence of impermissible hindsight, the prior art regimen of 1 to 4 times per day, does not suggest an interval between consecutive doses. As such, Tyers fails to suggest an

interval of 0.5-4 hour intervals between at least two consecutive administrations as recited by the claimed invention.

B. The claimed invention provides a 20%-30% improvement in the inhibition of acid secretion.

On page 2 of the final Office Action, the Examiner states that Figure 1 of the specification shows a "slight *increase*" in the percent inhibition of acid secretion. Thus, the Examiner agrees that the claimed invention does indeed provide an improvement in the inhibition of acid secretion. Applicants disagree, however, that the improvement is "slight".

As described in the Example, the pharmacological effect of the claimed invention was compared with a conventional administration regimen involving omeprazole. Pursuant to the invention, a first group of subjects received 20 mg of omeprazole twice daily with 3 hours apart from each administration. A second group of subjects received a single 40 mg daily dose of omeprazole. With each group of subjects, the efficacy of the respective administration regimen in controlling acid secretion was measured.

As shown in Figure 1, a 30% increase in inhibition and a 20% increase in inhibition was obtained with the claimed invention on days 1 and 2, respectively. Contrary to the Examiner's opinion, this increase represents a superior and unexpected advantage over the prior art.

The dramatic improvement in acid inhibition which is possible with the claimed invention represents an advantageous administration regimen in the treatment of gastric acid related disorders. Since it was known in the prior art that the duration of acid inhibition of a single dose of omeprazole is 3-4 days (See. p 2, lines 16-18), it was truly unexpected that the efficacy of omeprazole could be substantially improved by as much as 20%-30% by two or more consecutive administrations with 0.5-4 hour intervals. As such, the prior art is silent and shows

no appreciation of the possibility of achieving an improvement by two or more consecutive administrations of an acid labile H^+, K^+-ATPase inhibitor with 0.5-4 hour intervals.

The unexpected and superior improvement in acid inhibition represents a greater than expected result. It is precisely this type of "greater than expected result" which has long been an evidentiary factor pertinent to a finding of nonobviousness. (*United States v. Adams*, 383 U.S. 39, 51-52 (1966). For all of the foregoing reasons, withdrawal of the §103 rejection based on Tyers is requested.

V. Claim Rejection – 35 U.S.C. §103

Claims 1, 2 18, 26 and 27 remain rejected under 35 U.S.C. §103(a) in view of the combination of WO 96/01624 and Tyers. According to the Examiner, WO 96/01624 at page 10, lines 17-22, discloses that dosage forms comprising a proton pump may be administered one to several times a day. The Examiner relies on the alleged disclosure by Tyers of an administration regime of 1 to 4 times a day.

A. An administration regimen of one to several times per day is different from and does not suggest an administration regimen having 0.5-4 hour intervals.

Applicants respectfully submit the following:

- an administration regimen of one to several times per day is different from an administrative regimen having 0.5-4 hour intervals between at least two consecutive administrations; and
- in the absence of impermissible hindsight, an administration regimen of one to several times per day does not suggest an administrative regimen with 0.5-4 hour intervals between at least two consecutive administrations.

Applicants submit that the administration regimen as broadly disclosed by WO 96/01624, i.e., daily doses one to several times a day, is consistent with the typical administration regimen of many prescribed pharmaceuticals. In this regard, Applicants rely on the cited prior art reference to Martindale which teaches the administration of a single daily dose of omeprazole. Furthermore, in the absence of impermissible hindsight, an administration regimen of one to several times day does not suggest an administrative regimen with 0.5-4 hour intervals between at least two consecutive administrations.

B. The claimed invention provides a 20%-30% improvement in the inhibition of acid secretion.

As stated is Section IV, above, Figure 1 of the specification shows that a 30% increase in inhibition and a 20% increase in inhibition are recorded with the claimed invention on days 1 and 2, respectively. Since it was known in the prior art that the duration of acid inhibition of a single dose of omeprazole is 3-4 days (Seep.2, lines 16-18), it was truly unexpected that the efficacy of omeprazole could be substantially improved by as much as 20%-30% by two or more consecutive administrations with 0.5-4 hour intervals.

The unexpected and superior improvement in acid inhibition represents a greater than expected result. It is precisely this type of "greater than expected result" which has long been an evidentiary factor pertinent to a finding of nonobviousness. (*United States v. Adams*, 383 U.S. 39, 51-52 (1966).

For the reasons given in Section IV, above, the secondary reference to Tyers fails to overcome the deficiencies of WO 96/01624 to suggest the claimed invention. Whether taken alone or in combination, WO 96/01624 and Tyers do not suggest the claimed invention. Neither reference provides the required motivation to administer consecutive dosages separated by 0.5-4

hour intervals to advantageously obtain an unexpected and superior improvement in inhibition of acid secretion.

Withdrawal of the §103 rejection based on the combination of WO 96/01624 and Tyers is requested.

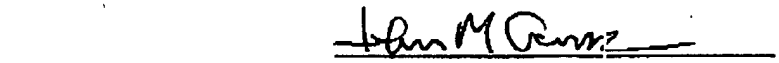
CONCLUSION

The claim amendments and remarks set forth herein are fully responsive to the Office Action. It is respectfully submitted that claims 1, 2, 18, 26 and 27 are in condition for allowance, which action is earnestly solicited.

Any additional fee in connection with this response should be charged to Deposit Account No. 23-1703.

Dated: November 20, 2003

Respectfully submitted,



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